REMARKS

Reconsideration of the application is respectfully requested in view of the above amendments and the following remarks.

Claims 56-73 were pending in the present application. Claims 61-72 were withdrawn from consideration by the Examiner as being drawn to the non-elected invention by the Examiner. Claims 56-60 and 73 are currently pending.

No new matter has been added to the above-captioned application by the amendments.

OBVIOUSNESS TYPE DOUBLE PATENTING REJECTION

The Examiner stated Claims 56-60 are rejected on the grounds of non statutory obviousness type double patenting as being unpatentable over Claims 1-5 and 8-11 of US 5, 908,830. The Examiner indicated that although the conflicting claims are not identical, they are not patentably distinct from each other because the present application teaches a composition comprising a NPY5 antagonist of formula I and a NPY1 antagonist, and US 5,908,830 teaches a composition comprising a metabolic rate modifying agent (such as a NPY1 antagonist) and a feeding behavior modifying agent (such as a NPY5 antagonist). The Examiner stated that the two components of the patent's composition are the same as the present application's composition, however the patent's components are broad and the present application's components are specific; therefore the patented application encompasses the present application.

Applicants respectfully disagree. Applicants submit that the claims of the present application and the claims of US 5,908,830 are patentably distinct.

The claims of US 5,908,830 and the present application differ in scope. US 5,908,830 claims the combination of a NPY5 receptor antagonist in general and a NPY1 receptor antagonist; whereas, the present invention claims a specific genus of NPY5 receptor antagonists of formula I, and species thereof, in combination with a NPY1 receptor antagonist. US 5,908,830 does not specifically disclose or teach the NPY5 antagonists of formula I of the present application, or the combination of the NPY5 antagonists of formula I and an NPY1 antagonist. It is possible to infringe claims 1-5 and 8-11 of US 5,908,830 and not to infringe claims 53-60 of the present application by using a NPY5 antagonist of a formula outside of the scope of the claims of the present invention.

The Examiner further indicated that Claim 56 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claim 1 of copending Application No. 11/429,721 (US 2006/0270650). The Examiner stated that the only difference between the present claims and the copending claims is that in the copending claims an additional agent is administered with the presently claimed active agents.

Applicants respectfully disagree. Applicants submit that the claims of the present application and the claims of USSN 11/429,721 are patentably distinct. The claims of USSN 11/429,721 are directed to compositions comprising at least 3 components, one of which is calcium and/or xanthan gum. However, the present invention does not teach or disclose the use of calcium or xanthan gum as a component in the composition. The claims of the present invention are directed to compositions comprising a NPY1 receptor antagonist and a NPY5 receptor antagonist.

Applicants further submit that there is no overlap between either the amended or original claims of the present invention and the claims of US 5,908,830 or the pending claims of USSN 11/429,721. The compositions claimed in the present application are novel and are not suggested by US 5,908,830 and USSN 11/429,721. The Examiner has provided no motivation to modify the claims of USSN 11/429,721 to arrive at the presently claimed invention. Therefore no terminal disclaimer is required.

In view of the above arguments, Applicants respectfully submit that Claims 56-60 are adequately enabled and request reconsideration and withdrawal of the rejection of Claims 56-60 under 35 USC 112, first paragraph.

REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH
FOR LACK OF ENABLEMENT

The Examiner rejected Claims 56, 57 and 73 under 35 USC 112, first as failing to comply with the written description requirement. The Examiner stated that Claims 56, 57 and 73 describe compounds that are NPY1 antagonists, and cover all compounds having the pharmaceutical property of being a NPY1 antagonist to treat obesity. The Examiner further stated that describing a compound by its

functions will not substitute for written description of the structure of the compound. Finally, the Examiner stated that the specification does not enable any person skilled in the art to make or use the invention commensurate in scope with these claims.

Applicants respectfully disagree. Applicants submit that rejected Claims 56, 57 and 73 of the present application are described in the specification in such a way as to enable one skilled in the art to practice the invention.

The present invention refers to synthetic methods in the disclosed patent applications for the NPY5 antagonists of formula I on 1) page 21, lines 27-29, 2) page 22, lines 7-9, and 3) page 29 line 16 to page 30 line 3, and for the NPY1 receptor antagonists on page 31, lines 29-34. These referenced patent applications show how to make the disclosed NPY5 and NPY1 receptor antagonists. Applicants submit that the disclosed patent applications sufficiently describe how the disclosed NPY5 and NPY1 receptor antagonists can be made and that one of ordinary skill in the art would be able to make the compounds of the present invention based on the disclosures in the referenced applications.

Applicants further submit that the specification discloses how to use the compounds of the present invention. The specification discloses a method for determining which anti-obesity agents, including which NPY1 receptor antagonists, are useful in the present invention on page 30, lines 4-38. Examples 3 and 4 on pages 64 to 65 of the specification disclose how to test and use the combination of a NPY5 receptor antagonist and a second anti-obesity agent, such as a NPY1 receptor antagonist. The specification also provides a statement of the utility of the claimed compounds on page 46, line 30 to page 47, line 24. The specification specifically discloses that the anti-obesity agents, such as NPY1 receptor antagonists, in the compositions and methods of the present invention are useful to treat obesity and obesity related disorders.

The specification further teaches how to use the NPY5 and NPY1 antagonists by including a detailed description of routes of administration and dosages. Specifically, the dosage ranges of 0.0001 mg/kg to 100 mg/kg of body weight are listed on page 52, line 5 to page 53, line 30; and the routes of administration for the compounds of the present invention are recited as "oral, rectal, topical, parenteral, ocular, pulmonary, and nasal" on page 55, line 24 to page 58, line 27. Applicants submit that the specification sufficiently describes how the compounds of the present invention can be used and sufficiently describes how and in what dosage the compounds of the present invention can be administered.

The Examiner stated that the specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation.

Applicants submit that the specification provides guidance that is sufficient for treating disorders, including obesity and obesity related disorders, and that would allow the skilled artisan to practice the instant invention without undue experimentation. The court has held that "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (*In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404 (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). One of ordinary skill in the art can readily identify the compounds of formula I useful in the methods of the present invention. As disclosed above, using the assays and criteria provided on pages 30 of the specification, one of ordinary skill in the art can readily determine if a compound, such as a NPY1 receptor antagonist, works as an anti-obesity agent and is useful in the present invention. Applicants submit that a reasonable amount of guidance with respect to experimentation is given in the specification.

The Examiner stated that the instant claims are very broad, for instance, Claims 56 and 73 are directed to a plethora of compounds described by functional properties and one of relative skill in the art, generally a Ph.D. or M.D, could not predict from the instant disclosure which compounds would fall under the umbrella of functional description of being known as NPY1 antagonists.

Applicants disagree. As previously noted, the utility of the NPY5 receptor antagonists of formula I and NPY1 receptor antagonists is disclosed in the specification on page 30 and in the art, including assays disclosed in the NPY1 receptor antagonist patent applications listed on page 31, lines 29-34. Additionally, Applicants assert that in vitro and in vivo testing of each embodiment of the invention is not required under section 112, first paragraph. Applicants submit that section 112 does not require working examples (*In re Strahilevitz,* 668, F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982)) and that the applicants' claim scope is not necessarily limited only to those embodiments actually disclosed in the specification (See *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); see also *Utter v. Hiraga*, 845 F.2d 998, 6 U.S.P.Q.2d at 1714 ("A specification may, within the meaning of 3 USC 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses"), and that the embodiment need not necessarily have even been reduced to practice (See In re Wright, 999 F.2d 1557; 1561, 27 U.S.P.Q.2d 1510, 1513).

Applicants further submit that although the claimed invention has not yet been tested in human clinical trials for safety and effectiveness, such trials are not required to establish utility under the patent law:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating the incentive to pursue, through research and development, potential cures in many crucial areas... *In re Brana*, 34 U.S. P.Q.2d 1436, 1442-3 (Fed Cir. 1995).

In summary, the instant specification provides a teaching of how to use the invention which would be credible to the person of ordinary skill in the art and which would permit the skilled artisan to use the claimed compounds for the stated utility without undue experimentation.

Finally, the Examiner indicated that Claim 57 covers all compounds having the pharmaceutical property of being known as a compound (NPY1 antagonist) to treat obesity. Applicants respectfully disagree. Claim 57 lists one specific NPY1 antagonist, J-115,814 and salts or esters thereof, and therefore does not require any additional experimentation to determine if a compound is a "NPY1 antagonist" since the structure and use of J-115,814 as a NPY1 antagonist was known in the art prior to the priority date of the present application (See Kanatani et al., Molecular Pharmacology, Vol. 59, No. 3, 501-505 (2001).

The Examiner also stated that the working examples are limited to the combination of a NPY5 antagonist derived from formula I combined with a NPY1 antagonist such as nalmefene or sibutramine only. Applicants submit that nalmefene and sibutramine are not NPY1 receptor antagonists.

In view of the above arguments, Applicants respectfully submit that Claims 56, 57 and 73 are adequately enabled and request reconsideration and withdrawal of the rejection of Claims 56, 57 and 73 under 35 USC 112, first paragraph.

REJECTION UNDER 35 U.S.C. 103(a)
FOR OBVIOUSNESS

The Examiner rejected Claims 56-60 and 73 under 35 USC 103(a) as being unpatentable over Fukami et al. (US Patent 6,326,375), in view of Kanatani et al. Molecular Pharmacology, Vol. 59, No.3, pp. 501-505 (2001), and in further view of De Lacharriere et al. (US 5,858,024).

The Examiner indicated that Fukami et al. teaches spiro compounds derived from the same formula I as set forth in Applicants' Claim 56, including Applicants' preferred spiro compound, 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H), 4'-piperidine]-1' carboxamide, and their use to treat metabolic diseases such as obesity. The Examiner stated that the instant invention differs from Fukami et al. in that Fukami et al. does not teach the addition of a second agent, a NPY1 antagonist such as J-115814; however, Kanatani et al. teaches J-115814 as an agent used to suppress the feeding appetites of obese mice, and produces the reduction of spontaneous food intake thus possessing anti-obesity activity. The Examiner stated that clearly one of skill in the art would have assumed the combination of two individual agents well known to treat obesity into a single combination would give an additive effect in the absence of evidence to the contrary.

Finally, the Examiner indicated that the De Lacharriere et al. reference teaches the first and second compositions are packages separately in the form of a kit, in an arrangement which is well known to those of skill in the art (column 2, lines 6-10). The Examiner stated that clearly, one skilled in the art would have been highly motivated to place the two individual agents in a kit since placing compounds in a kit is well known and old in the art.

Applicants respectfully disagree. Applicants submit that Fukami et al. (US 6,326,375) teaches the compounds of formula I, however, this patent does not teach or suggest the use of the compounds of formula I with a second anti-obesity agent, such as a NPY1 receptor antagonist. Given the disclosures and teachings of Fukami, one of skill in the art would not have been motivated to use a NPY5 receptor antagonist, in general, or a NPY5 receptor antagonist of formula I, in combination therapy with a NPY1 receptor antagonist to treat or prevent obesity or

an obesity related disorder. Therefore, the composition of a NPY5 receptor antagonist of formula I and a NPY1 receptor antagonist, and the use thereof to treat obesity or an obesity related disorder, is not prima facie obvious.

Applicants also submit that Kanatani et al. does not teach or suggest a composition comprising a NPY1 receptor antagonist, such as J-115814, and a NPY5 antagonist of formula I as a combination therapy to treat or prevent obesity or an obesity related disorder. There is no motivation in the Kanatani reference to use J-115814, or another NPY1 receptor antagonist, in a two component combination therapy with a NPY5 receptor antagonist of formula I to treat or prevent obesity. Therefore, the composition of a NPY1 receptor antagonist, such as J-115814, and a NPY5 receptor antagonist of formula I, and the use thereof to treat obesity or an obesity related disorder, is not prima facie obvious.

Finally, Applicants submit that although "kits" are known in the art, the present invention does not claim a generic "kit". Instead, the present invention claims a kit comprising specific active agents – a NPY5 receptor antagonist of formula I and a NPY1 receptor antagonist. De Lacharriere et al. discloses and claims a kit suitable for dyeing keratin fibers comprising 1) at least one substance P antagonist, and 2) a second composition comprising at least one dye, pigment or dye precursor exhibiting an irritant dye effect. De Lacharriere et al. does not teach or suggest a kit comprising a NPY1 receptor antagonist, either generally or specifically, and a NPY5 receptor antagonist, either generally or specifically a NPY5 receptor antagonist of formula I. There is no motivation in the De Lacharriere et al. reference to provide a kit comprised of a NPY1 receptor antagonist and a NPY5 receptor antagonist, in general or of formula I. Therefore, a kit comprised of a NPY1 receptor antagonist and a NPY5 receptor antagonist of formula I is not prima facie obvious.

As cited in the KSR opinion, "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results (See KSR International Co. v Teleflex Inc., 550 U.S. __ (2007) at 4; See also US v. Adams, 383 US 39, 50-52). Applicants submit that in the treatment of disorders associated with excessive food intake such as obesity, it is not predictable that combining an NPY5 antagonist of formula I and a NPY1 antagonist that works via a different biological mechanism will result in additional or additive weight loss or food intake reduction. The following references show the unpredictability of combinations of anti-obesity agents. The Wadden reference states that the addition of orlistat to

sibutramine did not induce further weight loss as compared with treatment by sibutramine alone (mean changes = +0.1 ± 4.1 kg vs + 0.5 ± 2.1 kg, respectively) (See Wadden et al., Obesity Research Vol. 8, No. 6, pp 431-437, Sept. 2000). The Wadden reference also states that the findings suggest that the combination of sibutramine and orlistat is unlikely to have additive effects that will yield mean losses ≥ 15% of initial weight, as desired by many obese individuals. Further, the Erondu reference states that blockade of the NPY5 receptor with MK-557 (a neuropeptide Y 5 receptor antagonist) did not increase the weight loss efficacy of either orlistat or sibutramine (See Erondu et al. Poster, NAASO, Obesity Society Annual Meeting, Boston, MA, October 2006). The Wadden and Erondu references are enclosed. Applicants submit that based on these references, one of ordinary skill in the art would not be able to predict whether any particular combination of anti-obesity agents would lead to synergistic or even additive weight loss.

Applicants hereby submit the Declaration under 37 CFR § 1.132 of Dr. Douglas John MacNeil, which discusses *in vivo* studies of the NPY5 receptor antagonist, L-753550, and the NPY1 receptor antagonist, J-115,814, combination and their results. In the Declaration, Dr. MacNeil states that in his opinion, one of ordinary skill in the art would have found it surprising and unexpected that the combination of L-753550 with J-115,814 dosing resulted in 1) synergistic body weight loss, and 2) a synergistic reduction of food intake.

Applicants respectfully submit that in view of the above arguments and study results, the composition comprising a NPY5 antagonist of formula I, such as L-753550, and a NPY1 antagonist, such as J-115,814, and a kit thereof, is not obvious over the Fukami, Kanatani and De references, and respectfully request reconsideration and withdrawal of the rejection of Claims 56-60 and 73 under 35 USC § 103(a).

Applicants believe that all of the rejections have been overcome and therefore earnestly solicit an early Notice of Allowance.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

MERCK & CO., INC.

By Pamela Spalding Date 10-5-07